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CONTENTS

ARTICLES IN *CA* ARE INDEXED IN INDEX MEDICUS AND SOME ARE ABSTRACTED IN CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, EXCERPTA MEDICA AND ABSTRACTS OF WORLD MEDICINE.

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Clinical Staging System for Cancer and End Results Reporting

Murray M. Copeland, M.D.

The clinical extent of disease is an important concept in staging tumors for purposes of treatment. The basic difficulty in the staging of any malignant tumor is human variation in describing the lesion on examination. Additional factors become most important from the standpoint of end results reporting. To bring a uniform standard of staging classification to fruition is fraught with difficulty, due to varying shades of opinion as to what factors should be used. Within the scope of debate are such factors as age, duration of the disease, size and accessibility of the tumor, and histologic type of disease. The necessity of some or all of these factors being included is evident in the continuing efforts to effect further diagnostic techniques and, indeed, to develop new methodologies in diagnosis.

As there are many forms of cancer, we must have detailed diagnostic criteria expressed in definitive terms, which are understood and agreed to by all concerned. We do not have a universally applicable form of therapy for all tumors, thus it is necessary to delineate and explore the effect of specific forms of therapy on specific forms of cancer, in specific stages of advancement. Records containing such complete data will offer a means of providing exchange of experience among investigators with comparable diagnostic criteria.

Historically, the practice of dividing cancer cases into groups according to so-called stages arose from the fact that the crude survival or apparent recovery rates were higher for cases in which the disease was localized than for those in which the disease had extended beyond the organ of origin. These groups were referred to erroneously as "early" and "late", implying some regular progression with time, which did not take place, in many instances. In the future, to avoid misinterpretation, it would seem wise to define the word "stage" as the apparent extent of disease when the patient is examined clinically, and "staging" as the division or classification of cancer cases into groups or categories by degree of apparent extent of disease according to some agreed plan.

The immediate goal of staging cancer cases is to facilitate an accurate, concise description of the apparent extent of disease in a way that can readily be communicated to others or reproduced by them. Such a goal implies the ultimate purpose of making a judgment as to prognosis and a decision as to an effective course of treatment.

It is undesirable to propose any classification which might limit further independent observation, restrict freedom in the presentation or analysis of data, or which would be difficult to change. What is needed is an agreement for each site, on the recording of accurate information concerning the extent of disease, so that it will be possible to combine or re-combine cases according to any agreed plan.

A physician who undertakes the care of a cancer patient makes his first treatment plan by visual inspection,

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physical examination and use of other diagnostic facilities, including biopsy examination of the primary lesion. In many cases, the clinical approximation may be the final one, as in patients who are to be treated by chemotherapy or radiotherapy. Radiologists feel it unfair to compare groups of cases reclassified after obtaining postoperative histologic information, with groups of patients in which such information is not available, because of a nonsurgical form of therapy.

These and many other basic problems have perplexed classification committees of both national and international organizations. At present, general interest lies in the area of clinical stage classification. The careful clinical description and classification of malignant neoplasms is felt to serve a number of objectives, such as: (1) Aiding the clinician in the planning of treatment; (2) giving some indication of prognosis; (3) assisting in the evaluation of the results of treatment; (4) facilitating the exchange of information between treatment centers; (5) assisting in the continuing investigation of human cancer.

One basic problem has been whether or not clinical staging for end result reporting should be used exclusively; or whether, in a statistical coding system, staging based on histologic proof of extent of disease should also be provided. Another problem has been whether this latter type of staging should be separate from or equal to the clinical staging in importance. It is certainly possible that cross-indexing of stages by histologic extent of disease with the clinical staging of cancer would add valuable information to a number of disciplines.

In 1954, the research commission of the Union Internationale Contre le Cancer activated a committee on Clinical Stage Classification and Applied Statistics under the chairmanship of Dr. Pierre Denoix of Paris. This committee, in effect, is a continuation of the Committee on Tumor Nomenclature and Statistics previously active since 1950, under the aegis of the U. I. C. C.

Between 1950 and 1959, the members of the Committee have been:

Baclesse, F.	Paris
Barajas-Vallejo, E.	Mexico D. F.
Bucalossi, P.	Milan
Copeland, M. M.	Washington, D. C.
Denoix, P. F. (Chairman 1954-1959)	Paris
Fischer, A. W.	Kiel
Hamperl, H.	Bonn
Harmer, M.	London
Hultberg, S.	Stockholm
Lima-Basto, E.	Lisbon
Logan, W. P. D.	London
McWhirter, R.	Edinburgh
Perry, I. (Chairman 1950-1954)	San Francisco
Racov, A. I.	Leningrad
Roxo-Nobre, M. O. (Secretary)	Sao Paulo
Sellers, A. H. (Secretary)	Toronto

The Classification Committee met in Paris in July, 1959, and devised a Clinical Classification for Malignant Tumors of the Breast under a system known as **T.N.M.** Under this system, the "extent of disease" is considered as a complex which is analyzed in terms of three components: First, the primary tumor designated by the letter **T**; second, the regional lymph nodes designated by the letter **N**; third, distant metastases designated by the letter **M**.

This system provides for precise description, identification and coding of the various components in the clinical extent of disease, and thus, from these elements, the **T.N.M.** clinical stage grouping can be achieved.

**Now in Houston, Texas.*

T. N. M. Categories of Malignant Tumors of the Breast

T = Primary Tumor

T1—Tumor of 2 cm or less in its greatest dimension
Skin not involved, except in the case of Paget's disease confined to the nipple
No retraction of nipple
No pectoral muscle fixation
No chest wall fixation

T2—Tumor more than 2 cm but not more than 5 cm in its greatest dimension
or Incomplete skin fixation (tethered or dimpled)
or Nipple retraction (in subareolar tumors)
or Paget's disease extending beyond the nipple
No pectoral muscle fixation
No chest wall fixation

T3—Tumor more than 5 cm but not more than 10 cm in its greatest dimension
or Skin fixation complete (infiltrated or ulcerated)

T3—*Cont'd*
or Peau d'orange present in the tumor area
or Pectoral muscle fixation (incomplete or complete)
No chest wall fixation

Note: Incomplete pectoral muscle fixation indicates that contraction of the pectoral muscle limits the mobility of the tumor. Complete pectoral muscle fixation indicates that contraction of the pectoral muscle abolishes the mobility of the tumor.

T4—Tumor of more than 10 cm in its greatest dimension
or Skin involvement or Peau d'orange wide of the tumor but not beyond the breast area
or Chest wall fixation

Note: The chest wall includes the ribs, intercostal muscle and serratus anterior muscle. It does not include the pectoral muscle.

N = Regional Lymph Nodes

N0—No palpable homolateral axillary lymph nodes

N1—Homolateral axillary lymph nodes palpable but movable

N2—Homolateral axillary lymph nodes fixed to one another or to other structures

N3—Homolateral supraclavicular or infraclavicular lymph nodes movable or fixed
or Edema of the arm

Note: Edema of the arm may be caused by lymphatic obstruction. In such circumstances lymph nodes may not be palpable.

M = Distant Metastases

M0—No evidence of distant metastases

M —Distant metastases, including skin involvement wide of the breast, involvement of the contralateral lymph nodes or breast and

M —*Cont'd*
all cases with clinical or radiographic evidence of metastases to lungs, pleural cavity, skeleton, liver, etc.

On behalf of the Union Internationale Contre le Cancer this clinical stage classification for malignant neoplasms of the breast is presented for use on a trial basis for five years:

Clinical Stage Classification of Breast Cancer

Stage I—Tumor of 5 cm or less (T1 or T2)
Skin fixation absent (T1) or incomplete (T2)
Nipple may be retracted (T2) or Paget's disease may be present (T1 or T2)
Pectoral muscle fixation absent (T1 or T2)
Chest wall fixation absent
No homolateral axillary nodes palpable (N0)
No distant metastases (M0)

Stage II—Tumor of 5 cm or less (T1 or T2)
Skin fixation absent (T1) or incomplete (T2)
Nipple may be retracted (T2) or Paget's disease may be present (T1 or T2)
Pectoral muscle fixation absent (T1 or T2)
Chest wall fixation absent
Homolateral axillary nodes palpable but movable (N1)
No distant metastases (M0)

Stage III—Tumor of more than 5 cm in diameter (T3 or T4)
or Skin fixation complete (T3) or skin involvement wide of tumor (T4)
or Peau d'orange present in tumor area (T3) or wide of tumor (T4)
or Pectoral muscle fixation incomplete or complete (T3)
or Chest wall fixation present (T4)
or Homolateral axillary nodes fixed (N2)
or Edema of the arm (N3)
or Homolateral supraclavicular or infraclavicular nodes movable or fixed (N3)
No distant metastases (M0)

Stage IV—Distant metastases present (M) regardless of the condition of the primary tumor and regional lymph nodes.

Stage Grouping

These four stage groupings are therefore designated by the T. N. M. symbols as follows:

Stage I—T1 N0 M0
—T2 N0 M0

Stage II—T1 N1 M0
—T2 N1 M0

Stage III—T1 N2 or N3 M0

Stage III—*Cont'd*
—T2 N2 or N3 M0
—T3, N0, N1, N2 or N3 M0
—T4, N0, N1, N2 or N3 M0

Stage IV—Any combination of T and N symbols including M.

The above classification has obviously created differences of opinion as to the specifics of this classification, an aspect which is healthy and engenders necessary caution. Surgeons insist on pathologic extent of disease for end result reporting, whereas radiologists consider this unfair and urge use of pretreatment, clinical staging of disease. In the United States, these and other facets of disagreement have stimulated the establishment in 1958, of an American Joint Committee for Cancer Staging and End Result Reporting.* This Committee had its first formal meeting in Chicago, January 1959. The current members of this committee are as follows:

Murray M. Copeland, Chairman (American College of Surgeons) (ad hoc committee), Houston, member; Anthony R. Curreri (American College of Surgeons) (ad hoc committee), Madison, member; Danely P. Slaughter (American College of Surgeons), Chicago, alternate; Theodore P. Eberhard (American College of Radiotherapy) (ad hoc committee), Ann Arbor, member; Howard B. Hunt (American College of Radiology), Omaha, member; William T. Moss (American College of Radiology), Chicago, alternate; W. A. D. Anderson (College of American Pathologists), Miami, member; William O. Russell (College of American Pathologists), Houston, member; Paul R. Cannon (College of American Pathologists), Chicago, alternate; Samuel G. Taylor, III (American College of Physicians), Chicago, member; Alfred Gellhorn (American College of Physicians), New York, alternate; David A. Wood (American Cancer Society), San Francisco, member; Wendell G. Scott (American Cancer Society), St. Louis, alternate; Louis B. Thomas (National Cancer Institute), Washington, D. C., member; Robert Smith (National Cancer Institute), Washington, D. C., alternate.

The American Joint Committee agrees with many of the principles laid down by the U.I.C.C.'s Committee. They believe, however, that, if desired, freedom to use such factors as histologic proof of disease should be permissible in determining the extent of disease for end result reporting. The Committee also feels that freedom of clinical grouping is essential except, perhaps, for the purpose of international statistics. The Joint Committee, at its subsequent meetings has attempted to adhere to the **T.N.M.** categories of extent of disease, wherever possible, in order to facilitate rapprochement between the two committees.

The Southern Surgical Association, by resolution, has voted its approval of the objectives for which the American Joint Committee was founded, namely:

(a) To formulate a system of cancer staging and end result reporting which will be acceptable to the American medical profession and actively employed in cancer control; and (b) with the long-term objective that the American system be adopted in this country, hoping that many of the unacceptable facets in the U. I. C. C.'s cancer staging will be influenced by the American system.

The American Joint Committee appreciates the support of the Southern Surgical Association.

Subcommittees, designated as Task Force Committees, have been approved by the American Joint Committee to consider malignant neoplasms of appropriate anatomical sites. These subcommittees now have under advisement malignant tumors of the breast, larynx, prostate, bladder, uterine cervix and malignant diseases of the lymph nodes.

*Receives financial support from American Cancer Society and the National Cancer Institute.

At the present time, the classifications which have been formulated are being applied in selected clinics to determine the workable validity of the individual classification. The next meeting of the full committee will be held early in 1961, when it is hoped that the classifications, covering the various pathologic entities mentioned above, will be in final form for submission to the parent organizations. With their approval, the Joint Committee will have the authority to disseminate the classifications to the medical profession. These classifications will be subject to review, at periodic intervals, by the Committee. Many other primary anatomical sites of cancer are expected to come under review in the near future.

Further information on the American Joint Committee can be obtained from James B. Mason, M.D., Secretary of the Joint Committee and Assistant Director of the American College of Surgeons, 40 East Erie Street, Chicago, Illinois.

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The Rationale of Endocrine Therapy in Breast Cancer

Milton Dworin, M.D.

Cancer of the breast is the leading cause of death in women 40 to 60 years of age and represents 21.7 per cent of all malignancies in females.[9] At the present time about 70 per cent of women with cancer of the breast will need palliative therapy for advanced, recurrent, or metastatic breast cancer at some period in the course of their disease. It is readily apparent that this represents a problem of major magnitude in cancer management.

The purpose of this paper is to outline the historical development and the rationale for hormonal therapy, whether achieved by chemical or surgical means, in the palliative treatment of disseminated cancer of the breast.

Beatson in 1896 was the first to demonstrate that oophorectomy could induce temporary regression of metastatic mammary cancer.

In 1916 Lathrop and Loeb showed that in a cancer-bearing strain of mice the removal of the ovaries before the age of six months significantly lowered the incidence of cancer of the breast.

In 1932 Lacassagne produced cancer of the breast within six months by injecting estrin into the male mice of a strain in which the females had a high incidence of spontaneous mammary cancer.

Murray, four years earlier, using a strain of mice in which cancer of the breast developed in 80 per cent of the females but in none of the males, had found that after castration and implantation of an ovary, the incidence in the males rose.

In 1939 Woolley, Fekete and Little noted the return of irregular cycles of estrus in mice that had been spayed the day of birth. They hypothesized that the adrenal glands secreted the responsible estrogenic chemical.

Gardner in 1941 noted the development of vaginal and uterine epithelial changes compatible with estrogenic activity in spayed mice. Some of the animals were also noted to have developed adrenal tumors.

At the clinical level, Herrell in 1937 found the incidence of cancer of the breast after bilateral ovariectomy to be 1.5 per cent in 1,906 patients, while in a control group of 1,011 women of similar age, it was 15.4 per cent.

In 1947 Horsley reported a higher incidence of five-year cures in those women treated initially by radical mastectomy and bilateral ovariectomy, as compared to those treated by radical mastectomy only.

Loeser and Ulrich in 1939 independently reported on two cases each that appeared to be benefited by androgen therapy. Others followed, using androgens clinically in breast cancer. Because of the significance of this advance in cancer research, a Subcommittee on Steroids and Cancer was established by the Council on Pharmacy and Chemistry of the American Medical Association, with the object of coordinating the clinical studies on androgens by the many investigators (Council on Pharmacy and Chemistry, 1947, 1949, 1951).

Estrogens, originally regarded as im-

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portant factors in the development and growth of breast cancer, were first demonstrated in 1942 by Badger et al. to have an inhibitory effect on established lesions as well.

On the theory that the cancer was again activated by fresh hormones released from elsewhere in the body, Huggins[12] in 1951 performed adrenalectomy in addition to castration.

The control of cancers by hormonal means rests on two principles of medicine as stated by Huggins.[11] First, cancer is not necessarily autonomous and intrinsically self-perpetuating, and second, cancer can be sustained and propagated by endocrines that are functioning at normal or even subnormal levels. Those cancers retaining characteristics of the normal cells from which they arose in such a degree that the tumor cells function like the tissue of origin are, by definition, dependent tumors. These principles have led to the investigation of the therapeutic use of ablation of endocrine organs by surgery or by medication to suppress or neutralize endogenous hormones.

This close relationship between tumor growth and hormonal balance has led to the working hypothesis that an endogenous abnormality of steroid hormone metabolism may be responsible for the initiation and/or maintenance of tumor growth. It is this concept that has provided the stimulus for so much work in recent years. The efforts to unravel the relationship between steroid hormones and neoplastic disease have been exerted in two principal areas; steroid hormone metabolism in diseases of those tissues that are normally involved with steroid hormone synthesis, and the more general problem of disordered steroid metabolism in neoplastic disease of tissue not involved in hormone biogenesis. While progress in the first area has been impressive and has led to new and important conceptual and therapeutic advances, this cannot yet be said for the general problem.[3]

The indications for hormonal control of mammary cancer are: (a) For advanced primary lesions beyond conventional methods of therapy, (b) as an adjunct to other established methods, particularly when the disease is widespread, and (c) as a secondary procedure for treated, but recurrent or metastatic, carcinoma.

What then is the rationale with our present knowledge for the beneficial effects produced by modifying the hormonal "milieu intérieur", either chemically or surgically?

Oophorectomy

The relationship between the mammae and the ovaries was keenly appreciated by Thomas Beatson (1896), a Glasgow surgeon, who 63 years ago performed oophorectomy in human breast cancer patients on the assumption that since the ovary controls the normal mammary epithelium, it might also control cellular proliferation in cancers arising from this epithelium. It is generally agreed that the most plausible reason for the effectiveness of castration in advanced breast cancer is the withdrawal of some specific stimulating effect that estrogens or unknown ovarian hormones have on the abnormal, as well as the normal cells of the mammary gland. There is also the possibility that eradication of the ovarian steroids will permit hormones of other endocrine organs, particularly the adrenal glands, to exert an effect on the tumor. Halberstaedter and Hochman speculate that the withdrawal of estrogens probably diminishes the vitality of the malignant cell, giving the natural defenses of the body an opportunity to overcome the tumor cells.

Pearson and his associates[24] have

presented evidence which indicates that oophorectomy induces improvement by removal of the major endogenous source of estrogen. Thus, in selected patients who had improved after castration, administration of estrogen caused a reactivation of tumor growth, and withdrawal of the estrogen was followed by remission. Progesterone administration in these same patients had no measurable effect on tumor growth. It was concluded that approximately 50 per cent of these women had estrogen-dependent mammary cancer, whereas the rest had nonestrogen-dependent tumors. These observations would seem to provide a physiologic concept for therapy.

No practical means of selecting patients for oophorectomy, however, has been found. Neither the histologic picture, nor any clinical manifestations of the disease has been helpful in predicting a favorable response.

Androgens

The mechanisms by which androgen induces remissions in patients with breast cancer are not known. It has been considered that androgen may neutralize the effect of estrogen, although no direct evidence has been obtained to support this hypothesis. If this is the mechanism of androgen action, it does not appear to be an efficient neutralizing agent, since androgen is effective in only about one half of the patients with estrogen-dependent mammary cancer.

Farrow and Woodard, and Myers and his co-workers have demonstrated that androgen may accelerate the growth of mammary cancer in some patients. Estrogen also accelerated the growth of the tumor in the same patients. West and others have demonstrated that testosterone can be metabolized into estrogenic substances in castrated, adrenalectomized women with breast cancer. This conversion of androgen into estrogen in the body offers a possible explanation of the mechanism of androgen acceleration of tumor growth and why androgen fails to benefit some patients with estrogen-dependent mammary cancer.

It has also been postulated that the ameliorative effects of androgens and estrogens may be due to the fact that, in massive doses, these hormones depress pituitary function and produce a "chemical hypophysectomy."

Certain workers attribute the entire action of androgens in cancer to their effects on calcium metabolism, alkaline-phosphatase stimulation and osteoblastic activity. This is challenged by Sylvén and Hallberg, who postulate a central-nervous-system effect of androgen that might alter the pain threshold and thus relieve bone pain.

It can be theorized that castration, and estrogen and androgen administration under certain circumstances enhance an inherent defense reaction that in itself is not capable of reversing the course of a progressive breast cancer. Evidence in favor of this hypothesis is seen in cases in which regression of the lesion continues when treatment is discontinued before the maximal response has been obtained.

Because of the anabolic effect of androgen therapy, patients very frequently feel stronger, have improved appetite and hemograms, and gain weight. Improvement in these respects must not, however, be interpreted as evidence of tumor regression.

Estrogens

The mechanism by which estrogen induces remissions in women with breast cancer is unknown. It has been suggested that estrogen may induce beneficial effects indirectly by suppression of pituitary function or perhaps by

direct action on the tumor. In a few patients whose disease had relapsed or failed to respond after hypophysectomy, estrogen administration produced no measurable effects on tumor growth.

It has been well established that estrogen administration can accelerate the growth of breast cancer in some women.[26] Some breast cancers may have a dual dependence upon hormones, e.g., estrogen and a pituitary hormone. Thus, it is possible that estrogen might have dual effects on the growth of the cancer; one to stimulate and the other to suppress, of which either effect might predominate. These theoretical considerations offer a possible explanation for the apparent paradoxical effects of estrogen in patients with breast cancer. As stated before, the mechanism of estrogen therapy is unknown, although some investigators attempt to explain it on the basis of anterior pituitary suppression rather than on the basis of direct action of estrogen at the cell level.

Progesterone

Progesterone may also inhibit pituitary gonadotropin and corticotropin and can act directly upon the mammary gland to interfere with hyperestrinism without the adverse masculinizing effects of androgen therapy. Animal experiments suggested that progesterone might be of value on a therapeutic (Heiman, 1945; Noble and Collip) or prophylactic basis (Heiman, 1945). Loeser implanted 2,400 to 2,800 mg of progesterone in two patients with far-advanced metastatic breast cancer. Although their menses ceased, the progress of the disease was not altered. A preliminary report (Council on Pharmacy and Chemistry, 1951) on the use of progesterone in 11 patients revealed that one patient had a good subjective response, and one had soft-tissue-lesion and bone lesion regression. The other patients were not benefited. Further studies with progesterone to date have been disappointing.

Cortisone, Hydrocortisone, Prednisone and Prednisolone

Cortisone and hydrocortisone have been used in pharmacologic doses in attempts to produce tumor regression in cancer of the breast. It has been postulated that these drugs might produce sufficient suppression of the adrenal cortex making it possible to obtain the same beneficial effects as surgical ablation of the gland.

How these beneficial effects are produced by the adrenal cortical hormones and their analogues is not well understood. One action undoubtedly is that of blocking the normal tissue reaction against the foreign invasive process, thereby reducing edema, swelling and inflammatory cell infiltration.

Cortisone produces severe adrenocortical atrophy, presumably because of inhibition of ACTH secretion, and simultaneously stimulates the ovaries through augmentation of pituitary follicle-stimulating hormone excretion. When the ovaries are removed, the estrogen suppressive action of cortisone will be manifest.

The therapeutic use of cortisone as an anti-estrogenic agent is handicapped by its partial conversion into androgenic (and possibly estrogenic) substances, when the dose exceeds 100 mg per day.[17]

Thyroid supplementation when cortisone is used appears to have definite effects in prolonging remissions, either through its synergistic inhibitory effect upon the adenohypophysis or through its peripheral metabolic action in preventing unfavorable tissue changes, such as local myxedema.[16]

Adrenalectomy and Oophorectomy

Bilateral adrenalectomy for metastatic mammary cancer was introduced and successfully carried out by Huggins[12] in 1951. This was made possible by the discovery of cortisone, which enables one to provide adequate maintenance therapy. Huggins observed that the human adrenal gland could secrete sufficient quantities of growth-promoting steroids to maintain dependent neoplasms. It was also known that steroids from the adrenal cortex in patients with tumors or hyperplasias of this organ promoted the growth of secondary sex structures and that these steroids are produced in certain women after the menopause. In addition, Ingle was able to retard the growth of Walker carcinoma 256 in force-fed ovariectomized rats by adrenalectomy. It was noted that the adrenal glands of patients previously castrated may be enlarged and that increased amounts of estrogenic substances frequently were found in their urine. With these theoretical considerations and experimental observations, Huggins successfully introduced adrenalectomy without prohibitive morbidity or mortality.

Hypophysectomy

Following hypophysectomy, profound atrophy of the accessory sex organs occurs. It has been postulated that since estrogenic hormones, androgenic hormones and growth hormones are, under certain physiologic conditions, stimuli to the growth of mammary cancer, removal of the pituitary gland should eliminate these stimulating factors and induce another hormonal imbalance. Following removal of the hypophysis in man, adrenal insufficiency develops, unless treated with steroids, and myxedema requiring thyroid therapy usually appears in several weeks. In addition, various degrees of diabetes insipidus develop, requiring pitressin therapy.

Luft and Olivecrona[19] were the first to report a remission from hypophysectomy in a patient with advanced breast cancer. In a subsequent report,[20] these authors obtained improvement in 17 of a selected series of 30 patients with breast cancer. Since the ovaries and adrenal glands had not been removed from their patients, it could not be determined whether the remissions resulted from suppression of ovarian and adrenal function consequent to hypophysectomy, or whether removal of pituitary hormones was, in part, responsible for the improvement.

Pearson and his associates[25] were the first to demonstrate objective remissions in women with metastatic breast cancer who had previously undergone oophorectomy and adrenalectomy. In one of these patients who obtained a remission following hypophysectomy, administration of beef pituitary growth hormone appeared to produce a transient exacerbation of tumor growth in bone, as measured by calcium excretion.

These observations suggest that some breast cancers may be dependent upon pituitary hormones for growth. It is possible that some of the castrated, adrenalectomized patients had accessory adrenal glands and that the improvement following hypophysectomy may have been due, in part, to the suppression of function of these accessory glands.

Since hypophysectomy induces profound suppression of the function of the ovaries and adrenal glands, it is theoretically possible that this procedure may produce a summation of the beneficial effects of oophorectomy, adrenalectomy and hypophysectomy performed in sequence.

Conclusion

Thomas Beatson, the Glasgow surgeon, wrote in 1910: "One of the values attached to oophorectomy [now also true for hormonal and other ablative measures] is that the effects produced seem to me to have their chief interest and importance in that they throw a light upon the nature of carcinoma as a disease."

We are still profoundly ignorant of the real nature of hormone dependence in cancers arising in organs which are themselves hormone-dependent, but it probably is safe to assume in the case of hormone dependent breast cancer that the hormones essential for progressive proliferation of the cells of this tumor are those produced under physiological conditions for normal mammogenesis. It may be that these physiological hormones are produced by the cancer patient in excessive quantities, or in unphysiological proportions. It may even be that the normal mammogenic hormones are changed or modified by the breast cancer patient, but there is liter ally no evidence either to support or to disprove these purely hypothetical conceptions.

It is abundantly clear, however, that the intelligent investigation of hormone dependence in cancer, as well as its rational treatment by endocrine ablation, must be based upon our knowledge of breast physiology and especially of the complex interplay of those hormones which control the proliferation by mitosis of normal mammary epithelium.

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. . . And Then There Was "The Second-Look Operation"*

"Many a surgical neophyte, like myself, while reluctantly capitulating to the graduate school requirement to work at a problem of research found, in doing so, that it excited his interest, alerted his curiosity, and left him with a compelling impulse to continue investigative research. Often a man has stayed in the game, finding the pursuit of unanswered problems very satisfying to his soul.

The American language, I feel, stands in great need of a good word to connote the transition from rejection to acceptance. It is a common phenomenon with all of us. What seemed like an almost insurmountable obstacle course turned out to be a blessing in disguise.

I am, too, a product of this type of philosophy. Had it not been for my father's insistent persistence, I probably would have ended up a farmer, which I had always wanted to be.

One spring, while I was still a student in high school, we had on the farm about 50 sows that could not farrow their young. The first two sows with their unborn litters we lost while waiting, on the advice of our veterinarian, 'for nature to take its course'. I scurried through the *Breeders' Gazette*, *The Farmer*, and several books on the veterinary problems of the farmer which occupied a row on our modest book shelves. A snaring apparatus procured through the advertising columns of one of these journals proved useless. Much to my amazement, I found my own hand the best instrument to deliver these pigs. The effort cost me about 3 weeks of school, for as those of you who have had obstetrical experience know, such assignments are time-consuming, especially for multiple births. For me it was a task that had to be done. I can still feel, after these many years, the warmth of my father's sense of pride in the accomplishment. Three years in college went by before I capitulated to his pleas to have a go at medicine. That last summer on the farm, during World War I, when help was very scarce, it fell to my lot to haul manure every day for about 3 weeks during a hot spell between haying and harvesting. Well, it was too much. Anything, I thought, would be better than this! So through the portals of pigs and manure, I come before you tonight."

Speech originally reprinted by Medical Education Forum. *Wangensteen, O. H.: Education of a surgeon. Med. Ed. Forum Vol. 35, October, 1960; p. 971.*

**Dr. Owen H. Wangensteen, Professor and Chairman, Department of Surgery, University of Minnesota School of Medicine, developed this operation for cancer which demands a most determined physician and a trusting patient.*

On the Use of Fluorescence Technique in Exfoliative Cytology

Winifred Liu, M.D.

Theoretical Background

The recent application of fluorescence technique to exfoliative cytology employs fluorochrome acridine orange (AO) to stain the cells, and ultraviolet radiation as illumination. Acridine orange not only has a special affinity for nucleic acids in the cells, but also the ability to differentiate the two types of nucleic acids by fluorescing different colors under the ultraviolet excitation. When AO is combined with desoxyribose nucleic acid (DNA), the fluorescence is yellowish-green. When AO is combined with ribose nucleic acid (RNA), the fluorescence is orange-pink. Therefore, the nuclear material (AO-DNA) fluoresces a yellowish-green and the cytoplasmic granules and nucleoli (AO-RNA) fluoresce an orange-pink. The intensity of each depends on the concentration of nucleic acids.[2,5,6]

Theoretically, in fast-growing cells where there is a high concentration of RNA in the cytoplasm, the orange-pink cytoplasmic fluorescence is increased. In atypical and malignant cells where there is an abnormally high content of DNA in the nuclei as well as increased RNA in the cytoplasm, the nuclear fluorescence is remarkably bright and the cytoplasmic fluorescence is brilliant. The technique should be useful in detecting abnormal cells in rapid screening of cytologic smears.[1,3,4,9,10]

Practical Experience

A double-blind parallel study of routine gynecologic smears was conducted to compare the efficacy of the fluorescence method with Papanicolaou cytodiagnosis.[7,8] From the beginning of this study, three things became evident: (1) The increase of orange-pink fluorescence in the cytoplasm did not indicate cellular abnormalities; (2) the increase of yellowish-green nuclear fluorescence was nonspecific for cancer cells; (3) the brilliance of increased fluorescence obscured morphologic details in the cells. Therefore, no definitive cytodiagnosis could be made and the fluorescent smears were only classified into normal and abnormal categories.

During this study, 1,200 routine specimens were screened by the Papanicolaou method and 11 had a cytodiagnosis of cancer which was subsequently confirmed. In the fluorescence technique, only 10 of these 11 positive smears were classified as abnormal, a false negative error of one in 11. On the other hand, among all smears with a negative Papanicolaou cytodiagnosis, one in every five was considered abnormal by the fluorescence method. Therefore, a very high incidence of false positive as well as false negative errors occurred when using fluorescent smears.

In reviewing these fluorescent smears, the main difficulties seemed to be in the following facts: (1) Small parabasal cells with dense cytoplasm may show brick red fluorescence in the cytoplasm and brilliant yellow fluorescence in the nuclei, simulating malignant cells; (2) normal endocervical and endometrial cells frequently have brick red cytoplasmic fluorescence;

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(3) histiocytes are not easily identified from endometrial cells; (4) well differentiated small malignant cells may have only a normal degree of fluorescence.

Discussion

In evaluating the merits of the fluorescence technique in cytology, the discussion may be directed towards its three claims, namely: that it offers easy screening which results in an economy of time; that it allows employment of screeners with a minimum of training which results in an economy of skilled personnel; and that the method depends on cytochemical differences as well as morphological changes, therefore giving great accuracy even in very early cellular abnormalities.

I. Economy of Time

It was found that fluorescence technique offers no salvage of time. This is explained by the fact that a fluorescent smear is classified as normal only after careful screening of all the cells in the entire smear. This needs no less time than screening a Papanicolaou smear. Time may be temporarily saved with an abnormal fluorescent smear since such a smear is considered abnormal when the first abnormal cells are encountered. However, the same patient's Papanicolaou smear must be screened in its entirety for confirmation or rejection. In these cases, it is actually more time-consuming in establishing a cytodiagnosis, which is still based on the Papanicolaou method.

In addition, the finding of a few well-differentiated malignant cells in early cancers depends on the utmost vigilance and the sensitiveness of the eye to minor differences in fluorescence. Screening this type of fluorescent smear is equally as difficult as screening the same type of Papanicolaou smear.

Furthermore, in fluorescent smears, microorganisms fluoresce bright colors. Frequently, instead of forming a non-obtrusive background as they do in Papanicolaou smears, the bacterial flora may become a major component in fluorescent smears, at times even the most brilliant and prominent element. Therefore, what is gained with the fluorescence method by eliminating RBC's from the smear is offset by the even more bothersome and colorful fluorescence of the microorganisms.

This leaves only a small group of ideal smears which may be easily and safely screened by the fluorescence method. These same smears are equally easy to screen by the Papanicolaou method.

II. Economy of Skilled Personnel

From the foregoing discussion, it is hardly conceivable that individuals with a minimum of cytologic training could screen fluorescence smears better than they could Papanicolaou smears.

Furthermore, unlike many other laboratory tests, cytodiagnosis is in itself a definitive diagnosis. In most clinical tests, the data report the presence or absence of a factor which may or may not contribute toward a diagnosis. In cytology, however, the report of a negative smear actually states that the patient's specimen contains no malignant cells and, therefore, no cancer is present. This is a definite diagnosis, though negative. It seems most unjustifiable to rely on personnel with little training and skill to make such a major decision. Any trend toward a further reduction in personnel's training and understanding should be discouraged.

III. Accuracy

It was advocated that the fluorescence technique is based on cytochemical differences as well as morphological

changes and that it detects not only malignant cells but also very early cellular abnormalities. In evaluating this most important claim, the analysis may be directed to the fluorescence of the cytoplasm and the nucleus.

In the cytoplasm, as was described above, too often the normal cells fluoresce bright red while the well differentiated cancer cells may not. Moreover, when little or no cytoplasm is present, the cytoplasmic fluorescence cannot be relied on and the identification must depend on the nuclear interpretations alone.

In the nucleus, the fluorescence of malignant cells may be so bright that it glows and obscures the nuclear detail which may otherwise be seen. Furthermore, in benign, but hyperchromatic cells, equally brilliant nuclear fluorescence may be present. It is most difficult to distinguish a hyperchromatic benign cell from a hyperchromatic malignant cell in fluorescent smears. In addition, when a necrotic tumor is shedding degenerate cancer cells, there may be no apparent hyperchromasia and, therefore, no brilliance in the nuclear fluorescence. This type of malignant cell is not recognized during the screening of fluorescent smears.

Therefore, neither the described color and brilliance of fluorescence nor the classic morphological detail are considered reliable differentiating characteristics of abnormal cells in fluorescent preparations.

Conclusion

(1) The acridine orange fluorescence method used in exfoliative cytology does not save time or allow the employment of less skilled personnel. Most important of all, it lacks accuracy and cannot be relied on as a method for cytodiagnosis.

(2) At its best, it is hoped that the fluorescence technique may be used as a preliminary screening procedure before Papanicolaou screening. However, the nonspecificity of cellular fluorescence eliminates both normal and abnormal smears from being screened by the Papanicolaou method. Therefore, it is unsafe even for prescreening.

(3) In the present phase of the cancer campaign when cytology is beginning to be widely adopted with gratifying results, any modification of technique without good reasons will only bring confusion and defeat to the purpose of cancer education and control.

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Cancer Chemotherapeutic Agents

David A. Karnofsky, M.D.

Since World War II there has been an enormous increase in research, both in the laboratory and clinic, which has been directed toward the discovery of effective drugs against cancer. In 1955 the Cancer Chemotherapy National Service Center was established; it has greatly accelerated the search. During 1959, for example, the CCNSC spent $30,000,000 on this program. Research programs, with similar objectives, are functioning in many other countries, including England, France, Italy, Germany, Russia, Israel, India, Belgium, Holland, China, Hungary, Czechoslovakia and Japan. This high level of scientific activity may result in important discoveries at any time.

In September 1955, *CA* (5: 165-173) published tables of drugs considered to be useful in the management of advanced cancer and the indications for the use of these drugs. These tables have been revised and amended in 1961, six years later. [*See pages 60-66*—ED.] It is difficult to gain a correct perspective on certain recent developments, but they are noted because they may prove to be useful forms of treatment in certain situations.[3,7,11,12,18]

No polyfunctional alkylating agents of unique therapeutic value have been described in the past six years. Nitrogen mustard, chlorambucil, TEM and busulfan cover the needs of the vast majority of situations in which an alkylating agent is indicated.

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Among the antimetabolites, azaserine and DON have not proved to be of unique therapeutic value, and they have been dropped. 5-Fluorouracil has been added, although its therapeutic indications are not clearly defined. It has exhibited some therapeutic activity in large bowel, gastric, ovarian and breast cancers, and in hepatomas.[2,6,21]

A progesterone derivative (Delalutin)[13] has been added because of its reported effectiveness in metastatic adenocarcinoma of the uterus. Prednisone remains as useful as any other adrenal steroid preparation.

Among the miscellaneous drugs, new additions are Actinomycin D and o,p'DDD. Actinomycin D has a definite effect on pulmonary metastases in Wilms' tumor in children,[17] and it is an ingredient in the combined treatment of testicular tumors. The drug o,p'DDD has shown some effect on functional adrenal cancers.[1]

New uses of established drugs have been Amethopterin in choriocarcinoma in females,[14] and the combination, chlorambucil, Amethopterin and Actinomycin D in testicular tumors.[15]

New drugs now under clinical trial include various polyfunctional alkylating agents, purine and pyrimidine analogues, sex hormones and adrenal steroids, actinomycin derivatives, the antibiotics, Mitomycin C,[4] and Streptonigrin,[8] and the plant extract, Vincaleukoblastine.[9,10] The number of drugs suitable for clinical study is continually increasing.

There has been great interest in the regional administration of chemotherapeutic agents. The use of nitrogen mustard for recurrent effusions is well

established,[19] and intrathecal Amethopterin is effective in leukemic infiltration of the meninges.[20] Extracorporeal perfusion of isolated tumor-bearing areas,[5] and the continuous infusion of drugs into the arterial supply to a tumor have produced striking responses.[16] The practical indications for these techniques and the most effective of the available drugs have not been determined.

Clinical evidence, for most situations, does not support the prophylactic use of an alkylating agent following the removal of a resectable cancer, or the administration of chemotherapeutic agents to delay the progression of early metastatic cancer.

X rays are given in combination with chemotherapeutic agents for various reasons, but the clinical data suggesting that certain chemicals can potentiate the tumoricidal effects of local irradiation are not convincing.

Bone marrow transplantations to prevent the lethal effects of large doses of X rays or chemotherapy and thus permit more intensive therapeutic trials, are being widely discussed but data are again insufficient to justify the use of such procedures, except within clearly experimental circumstances.

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Specific Agents Used in Cancer Chemotherapy

	AGENTS	PRINCIPAL ROUTE OF ADMINISTRATION	USUAL DOSE	ACUTE TOXIC SIGNS	MAJOR LATE TOXIC MANIFESTATIONS
Steroid Compounds and ACTH	**Androgen**				
	Testosterone propionate	I.M.	50-100 mg. 3 x weekly	None	Fluid retention, masculinization.
	Fluoxymesterone (Halotestin®)	Oral	10-20 mg. daily		
	Estrogen				
	Diethylstilbestrol	Oral	1-5 mg. 3 x daily	Occasional N. & V.*	
	Ethinyl estradiol (Estinyl®)	Oral	0.1-1.0 mg. 3 x daily		Fluid retention, feminization, uterine bleeding.
	Progesterone				
	Hydroxyprogesterone caproate (Delalutin®)	I.M.	500 mg. 3 x weekly	None	
	Adrenal Cortical Compounds				
	Cortisone acetate	Oral	50-300 mg. daily	None	Fluid retention, hypertension, diabetes, increased susceptibility to infection.
	Hydrocortisone acetate	Oral	50-200 mg. daily		
	Prednisone (Meticorten®)	Oral	20-100 mg. daily		
	Adrenocorticotropic Hormone (ACTH)	I.V. I.M.	25-50 mg. by continuous infusion 10-20 mg. every 3 hrs.	None	
Radioactive Isotopes	Iodine (I^{131})	Oral, I.V.	100-200 mc.	None	Myxedema, bone marrow depression, renal damage.
	Phosphorus (P^{32})	Oral, I.V.	3-7 mc.	None	Bone marrow depression.
	Gold (Au^{198})	Intrapleur. Intracard.	75 mc. 75 mc.	None	Bone marrow depression.
	Methylbis (β-Chloroethyl) Amine HCl (HN2, Mustargen®)	I.V.	0.4 mg./kg. Single or Divided Doses	N. & V.*	

Polyfunctional Alkylating Agents				
Methylbis (β-Chloroethyl) Amine HCl (HN2, Mustargen®)	I.V.	0.4 mg./kg. Single or Divided Doses	N. & V.*	Therapeutic doses moderately depress peripheral blood cell count; excessive doses cause severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding. Maximum toxicity may occur two or three weeks after last dose. Dosage, therefore, must be carefully controlled. Alopecia occurs occasionally with cyclophosphamide.
Chlorambucil (Leukeran®)	Oral	0.1-0.2 mg. /kg./day	None	
Cyclophosphamide (Endoxan, Cytoxan®)	I.V. Oral	3.5-5.0 mg./kg./day x 10 (40-60 mg./kg. Single Dose) No Estab. Dose	N. & V.	
Triethylene Melamine (TEM)	I.V. Oral	0.04 mg./kg. x 3 20-40 mg. in 1 mo.	Occasional N. & V.	
Triethylenethiophosphoramide (TSPA, ThioTEPA®)	Oral I.V.	5-10 mg./day 0.2 mg./kg. x 5	None	
1,4-dimethanesulfonyloxybutane (Busulfan, Myleran®)	Oral	2-8 mg./day 150-250 mg./course	None	
Antimetabolites				
4-Amino-N10-methylpteroylglutamic acid (Amethopterin, Methotrexate®)	Oral	2.5-5.0 mg./day	None	Oral and digestive tract ulcerations; bone marrow depression with leukopenia, thrombocytopenia, and bleeding.
4-Aminopteroylglutamic acid (Aminopterin)	Oral	0.25-1.0 mg./day		
6-Mercaptopurine (6-MP, Purinethol®)	Oral	2.5 mg./kg./day	None	Therapeutic doses usually well tolerated; excessive doses cause bone marrow depression.
6-Thioguanine (6-TG)	Oral	2.5 mg./kg./day		
5-Fluorouracil (5-FU)	I.V.	15 mg./kg./day x 3-5	None	Stomatitis, nausea, GI injury, bone marrow depression.
Miscellaneous Drugs				
Urethane	Oral	2-4 gm. daily	N. & V.	Bone marrow depression.
Potassium arsenite (Fowler's solution)	Oral	0.2-1.0 cc. daily	None	Diarrhea, vomiting, skin eruptions.
Actinomycin D	I.V.	15 gamma/kg./day x 5	N. & V.	Stomatitis, GI disturbances, alopecia, bone marrow depression.
Demecolcin	Oral	5-8 mg./day	None	Alopecia, bone marrow depression.
o,p,'DDD	Oral	2-10 gm./day	N. & V.	Skin eruptions, diarrhea, mental depression, muscle tremors.

*Nausea and Vomiting

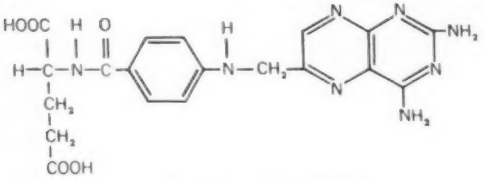
Neoplastic Diseases Responding to Chemotherapy

DIAGNOSES	POLYFUNCTIONAL ALKYLATING AGENTS	ANTIMETABOLITES	RADIOACTIVE ISOTOPES	STEROID HORMONES	MISCELLANEOUS DRUGS	RESULTS
Leukemia Acute, Children		6-MP Amethopterin		Adrenal Cortical Hormones		70% bone marrow improvement; 50% patients live one year or longer.
Acute, Adults		6-MP Amethopterin		Adrenal Cortical Hormones		15-25% improved for several months or longer.
Chronic Myelocytic	Myleran® HN2	6-MP	P^{32}		Demecolcin Urethane Fowler's solution	Patients maintained in good condition during major portion of disease; life occasionally prolonged.
Chronic Lymphatic	Chlorambucil TEM		P^{32}	Adrenal Cortical Hormones		Patients maintained in good condition during major portion of disease; life occasionally prolonged.
Hodgkin's Disease	Chlorambucil HN2 TEM			Adrenal Cortical Hormones		Occasional favorable response, but no definite prolongation of life.
Lymphosarcoma	Chlorambucil HN2 TEM			Adrenal Cortical Hormones		Occasional favorable response, but no definite prolongation of life.
Multiple Myeloma			P^{32} I^{131}	Adrenal Cortical Hormones	Urethane	Symptomatic relief in about 50% of cases, and objective hematological improvement in 15%.
Polycythemia Vera	Myleran® TEM HN2		P^{32}			Prolonged clinical remissions, particularly with P^{32}.
Carcinoma of Lung	HN2 TEM					Brief improvement in about 50% of cases.
Carcinoma of Ovary	TEM HN2	5-FU				30 to 50% of cases improved for one to three months, sometimes longer.
Carcinoma of Thyroid			I^{131}			Frequently marked improvement in properly selected cases.
Carcinoma of Breast	TEM HN2			Estrogens Androgens Adrenal Cortical		20 to 50% improved by hormonal therapy; life may be prolonged in some cases.

	HN2			Androgens Adrenal Cortical		some cases.
Carcinoma of Prostate				Estrogens		80% of cases respond to hormonal therapy; definite prolongation of life.
Wilms' Tumor	HN2				Actinomycin D	Temporary regression with 30% pulmonary metastases.
Choriocarcinoma, Female	HN2	Amethopterin				80% respond, of whom 30% show "permanent" regression.
Carcinoma of Colon		5-FU				15% respond for several months.
Carcinoma of Adrenal					o,p'DDD	Tumor regression and decrease in hyperadrenocorticism in selected cases.
Carcinoma of Testis	Chlorambucil*	Amethopterin*			Actinomycin D*	35% of patients show a favorable and sometimes prolonged response.
Miscellaneous Carcinomas and Sarcomas	HN2 TEM Chlorambucil Cyclophosphamide			Adrenal Cortical Hormones		In rare instances, favorable responses occur.
*Given in Combination						
Regional Cancer Chemotherapy						
Carcinoma in Facial Areas		Amethopterin + Citrovorum Factor (intraarterial infusion)				Favorable response of tumors supplied by external carotid artery.
Tumors of the Extremities	HN2 (extracorporeal perfusion)					Response in selected cases.
Pleural, Pericardial and Abdominal Effusions	HN2 (local instillation into appropriate cavity)		Au^{198} $CrP^{32}O^{4}$ (local instillation of drug into appropriate cavity)			About 25 to 50% of patients respond.
Leukemic Involvement Central Nervous System		Amethopterin (intrathecal injection)				About 80% of children with CNS involvement respond temporarily.

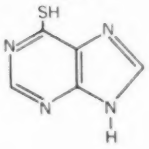
ANTIMETABOLITES

AMINOPTERIN



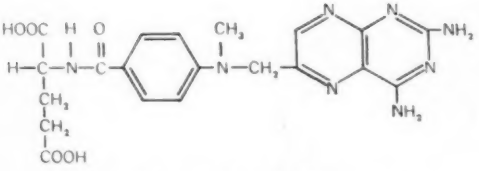
4-Aminopteroylglutamic acid

6-MP



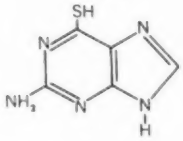
6-Mercaptopurine

AMETHOPTERIN



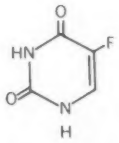
4-Amino N^{10} methylpteroylglutamic acid

6-TG



6-Thioguanine

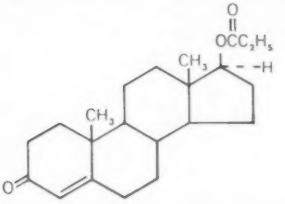
5-FU



5-Fluorouracil

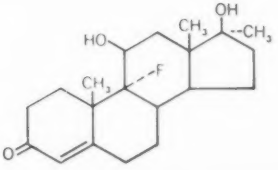
STEROID COMPOUNDS

TESTOSTERONE PROPIONATE



Δ^4-Androstene-17 β-propionate-3-one

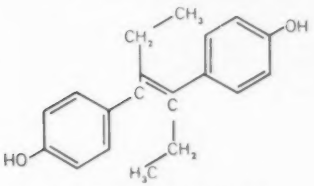
HALOTESTIN



9 α-Fluoro-11β-hydroxy-17α-methyltestosterone

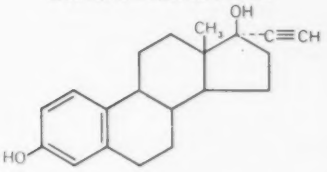
STEROID COMPOUNDS *continued*

DIETHYLSTILBESTROL



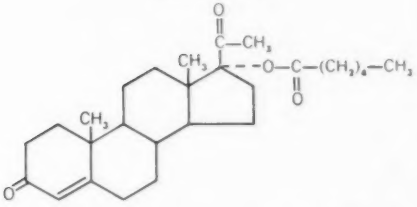
α,α' Diethyl 4,4' stilbenediol

ETHINYL ESTRADIOL



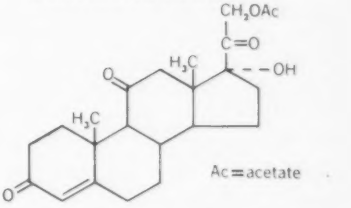
17 Ethinyl 3,17 dihydroxy Δ 1,3,5 estratriene

DELALUTIN



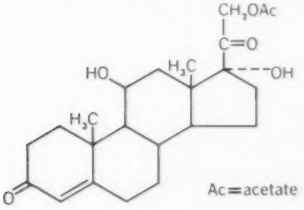
17α Hydroxyprogesterone hexanoate

CORTISONE ACETATE



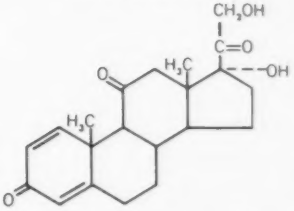
11 Dehydro 17 hydroxycorticosterone 21 acetate

HYDROCORTISONE ACETATE



17 Hydroxycorticosterone 21 acetate

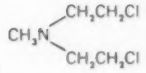
METICORTEN



Δ[1,4] Pregnadiene 17α ,21 diol 3,11,20 trione

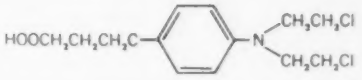
POLYFUNCTIONAL ALKYLATING AGENTS

HN2



methyl bis (β chloroethyl) amine

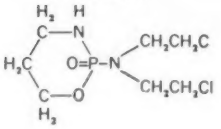
CHLORAMBUCIL



p di (β chloroethyl) aminophenylbutyric acid

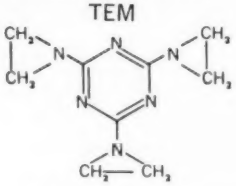
POLYFUNCTIONAL ALKYLATING AGENTS *continued*

CYTOXAN



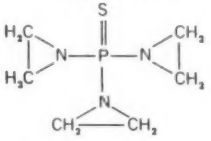
N, N-bis (β -chloroethyl)-N', O-propylene phosphoric acid

TEM



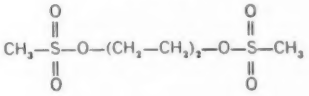
2, 4, 6-Triethyleneimino-s-triazine

THIO-TEPA



Triethylenethiophosphoramide

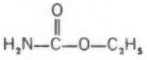
MYLERAN



1, 4-Dimethanesulfonoxybutane

MISCELLANEOUS DRUGS

URETHANE



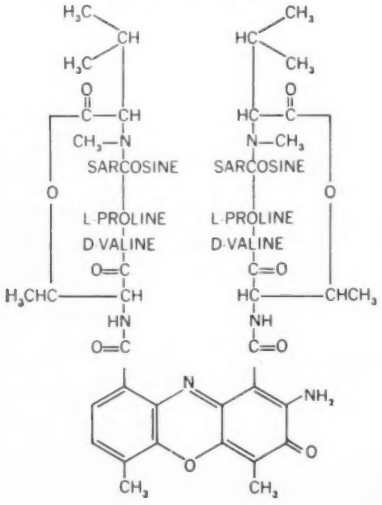
Ethyl carbamate

FOWLER'S SOLUTION

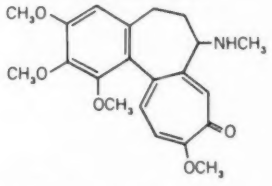
$KAsO_2$

Potassium arsenite

ACTINOMYCIN D

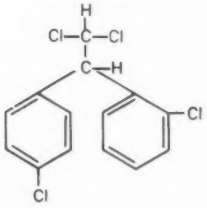


DEMECOLCIN



N-desacetyl-N-methylcolchicine

O, P'DDD



2,2-bis(4-chlorophenyl-2-chlorophenyl)-1,1-dichloroethane

Unproven Methods of Cancer Treatment

The following statement on Revici Cancer Control or lipid therapy, proposed by Emanuel Revici, M.D., Scientific Director of the Institute of Applied Biology and Trafalgar Hospital in New York City, was recently distributed to the 60 Divisions of the American Cancer Society for their information.

The Revici Cancer Control or lipid therapy, proposed by Emanuel Revici, M.D., Scientific Director of the Institute of Applied Biology (Trafalgar Hospital), New York, for the treatment of cancer and certain other conditions, is based on the belief that cancer is the product of imbalance between two types of lipids (acid and alkaline) in the tissues. This is reflected in the reactions of pain, pH of urine and tissues, etc., which are associated with changes in the acid-alkaline balance of the body. After determining the type of imbalance present in the tissues, patients are treated by adjusting the acid-alkaline level through administration of lipids or "liposides" which have an acid or alkaline reaction respectively. Dr. Revici describes this treatment of cancer as "biologically guided chemotherapy."

Since 1941, when this therapy first attracted attention in Mexico, many agents have been named by the proponents as giving promise at the moment in control of certain types of cancer reflecting an acid or an alkaline imbalance. Since, however, research is constantly being conducted, and new agents tested and substituted, no agent or agents to control either type of imbalance has been reported as an agent of choice for long. For instance, during one year, 1952, 17 different products, nine for treatment of acid symptoms, and eight for alkaline, were proposed for clinical trial to one group which was trying to reach agreement with the Institute on a plan for an evaluation study of this therapy.

Dr. Revici, a naturalized citizen of the United States, was born in Rumania in 1896, the son of a physician. He obtained his M.D. in 1920 at the Faculty of Medicine, Bucharest, and was licensed to practice medicine in New York in 1947. From 1921-26 he was Assistant Professor at the Faculty of Medicine, Bucharest; 1926-36, he directed his own research laboratory and practiced medicine; 1936-41, he was doing research in France at many hospitals and laboratories. In 1941 he fled from the Germans through Nice and Portugal to Mexico where he organized and directed the Instituto de Biológia Aplicada, A.C. in Mexico City till 1946. From April 1947 to the present he has been Scientific Director of the Institute of Applied Biology.

The Institute of Applied Biology was chartered April 1947 in New York as a nonprofit membership corporation, organized to conduct scientific and clinical research in cancer and allied diseases, and is entitled to tax exemption. Since 1955 it has been composed of three units: The Institute, 144 E. 90th Street; Trafalgar Hospital, 161 E. 90th Street, which is the headquarters' address, and the Basic Science Laboratory, 164 E. 91st Street. They occupy a nine-story 130 bed hospital, with facilities for laboratories and research, and a nearby four-story research laboratory. Their program is primarily focused upon research and the applica-

tion of results obtained to the treatment of hospitalized and outpatients. It is their belief that the need for frequent information about the "off balance" present and its degree of intensity requires strict supervision of treatment which is easier to obtain for hospitalized patients. The Institute formerly occupied smaller quarters without hospital facilities in Brooklyn at 54 Greene Avenue (1947-50) and 101 Lafayette Avenue (1950-55).

Until August 1957 it was supported by the Cancer Research and Hospital Foundation which was originally the Cancer Hospital Fund of Brooklyn. At that time, this group withdrew its support due to disagreement over administrative policies. A booklet issued by the Institute in 1960 names three groups as sources of support: the Cancer Control Project of the Institute of Applied Biology, a women's group which has been contributing for the past 10 years; the Variety Club of New York which organized the Cancer Control Research Foundation and adopted the work of the Institute of Applied Biology as its cancer research program in 1957; and the Gertrude Lawrence Foundation.

Since 1944, repeated attempts have been made by many individuals and groups to set up studies which would evaluate the claims made by the Institute of Applied Biology, and by supporters of the Institute and Dr. Revici, that therapeutic benefits, including reduction in size or disappearance of tumor, followed administration of the Revici Cancer Control. These have included the University of Wisconsin, the University of Chicago, the National Cancer Institute and the Committee on Cancer Diagnosis and Therapy of the National Research Council. In every case, it has been impossible to reach agreement with representatives of the Institute on procedures which would assure an objective scientific evaluation.

After careful study of the literature and other information available to it, the American Cancer Society has found no acceptable evidence that treatment with the Revici Cancer Control results in any objective benefit in the treatment of cancer in human beings.

NOW HEAR THIS

"In our series of 501 patients with rectal cancer, virtually all of the lesions could be palpated by means of simple digital examination. In fact, this cancer is so easily detected that 15 patients (3%) actually made their own presumptive diagnosis by palpating their own lesions."

WHO: **Dr. Victor A. Gilbertsen,** Assistant Professor, Dept. of Surgery, University of Minnesota School of Medicine, and Director, Cancer Detection Center.

WHERE: Minneapolis, Minn. Dec. 2, 1960. Faculty Club, University of Minnesota.

"When a student goes on for advanced work in physics, chemistry or electronics he enrolls in a graduate school. He receives a fellowship, often with a very satisfactory stipend. This training costs him little, if any, money. After a period of three to four years, if he stays in that long, he emerges with a Ph.D. degree, and by the time he is 27 or 28 years old he starts in on a job with a wonderful retirement program, five days a week of work, and a salary of $8,000 to $9,000 a year, at a time when a man preparing for medicine still has five to six years to go at a very inadequate stipend."

WHO: **Dr. John Z. Bowers,** Dean, University of Wisconsin Medical School.

WHERE: Wisconsin. May 4, 1960. House of Delegates, Third Session. State Medical Society.

"It is the duty of the scientist and physician to educate the less well-informed members of the community on matters of health; and at times he must play the role of crusader."

WHO: **Dr. Ralph Waldo Gerard,** Professor of Neurophysiology, University of Michigan.

WHERE: New York, N. Y. Jan. 15, 1961. Dartmouth College Convocation on "Conscience in Modern Medicine," broadcast over FM radio station WRVR.

"The stage of the disease at diagnosis is indicative of the public's awareness of the danger of delay in seeking medical care for ailments suggestive of cancer, and also, to some extent, the level of suspicion on the part of physicians in dealing with the disease. An average of 41% of all cases in the New York Medical College were localized during 1950-1958 inclusive, with marked improvement during the last four years, to a high of almost 49%, reflecting the significant decrease in cases with regional and distant spread."

WHO: **Dr. Walter L. Mersheimer,** New York College.

WHERE: Biltmore Hotel, New York, N. Y. Oct. 27, 1960. American Cancer Society Annual Meeting.

"Over ten million American women have viewed the American Cancer Society's film demonstrating the procedure of self-examination of the breasts. This effort has been most rewarding as shown by the fact that only 47.5 per cent of today's operable cases have axillary involvement, in contrast to 60 per cent 20 years ago."

WHO: **Dr. Frank E. Adair,** Attending Surgeon Emeritus, Memorial Hospital for Cancer and Allied Diseases.

WHERE: New York, N. Y. Jan., 1961. Memorial Hospital for Cancer and Allied Diseases.

"All smokers do not die of lung cancer because several diseases are competing with each other to cause the smoker's death. It's pretty hard to die of lung cancer if you already have died of coronary heart disease."

WHO: **Dr. Daniel Horn,** Director of Program Evaluation, American Cancer Society, Inc.

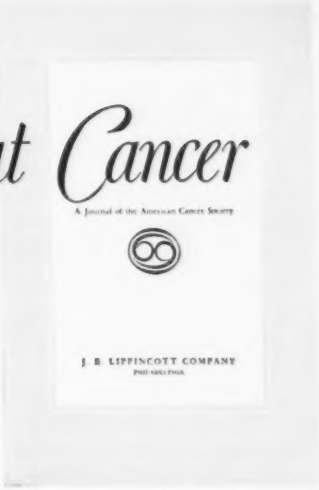
WHERE: New Jersey. Feb. 14, 1961. Bergen County Medical Society Meeting.

"Over 5,000,000 women in the United States had uterine cytologic examinations last year. This year pathologists expect to handle 6,000,000 cases. This capacity could be doubled in 1961, if necessary, by expanding existing facilities.

WHO: **Dr. David A. Wood,** Director, Cancer Research Institute, and Professor of Pathology, University of California.

WHERE: New York, N. Y. Jan. 19, 1961. American Cancer Society Board of Directors Meeting.

Looking at Cancer



A commentary on the March-April 1961 issue of CANCER, a journal of the American Cancer Society.

John W. Berg, M.D.
Associate Editor, Cancer

The problems of carcinoma of the vulva are considered by Gosling et al. in the light of the large experience of the University of Michigan Medical Center. This disease assumes an importance out of proportion to its relative frequency because diagnosis and treatment are so often delayed until heroic treatment is needed. In this series, for instance, the average time between the first symptom and the first medical consultation was more than a year; this was true even when the signal was a definite tumor growth rather than just exacerbation of a long-standing pruritus. Bowen's disease of this region is analyzed separately since it was found to be unique not only histologically but clinically. It occurred in younger women (typically vulvar cancer is a late postmenopausal disease), it tended to remain in situ for long periods, and it had a high rate of association with cancer of other sites. Granulomatous diseases were especially frequent in the patients' histories. On physical examination the indurated plaques, superficial excoriations, and verrucal lesions of Bowen's disease often were underrated so that biopsy was long delayed. The lesions tended to be multiple and widespread. For this reason, attempted conservative therapy of this "early" cancer did not always succeed even when involved areas were first delineated by multiple biopsies. There were three recurrences among nine patients conservatively treated, as compared with two among 13 patients whose more extensive disease was treated by vulvectomy. In the more common squamous cancers, the striking point was the gain in five-year survival from 24% before 1938 to 43% thereafter. This gain seemed partly due to earlier diagnosis but more to adequate therapy. Clinical node assessment was in error almost half the time; as a result, conservative therapy based on the hope of negative nodes was far less successful than excision plus node dissection (30% versus 60% five-year survival). Hence, routine "radical" surgery appears to be the procedure of choice.

The epidemiology and etiology of esophageal cancer is the subject of an extensive article by Wynder and Bross. Wide variations in incidence between races and sexes (esophageal cancer usually is a disease of men) could be explained largely by differences in the use of alcohol and tobacco. Together they produce a synergistic effect that accounts for about 80% of the esophageal cancer seen in this country. Hot and spicy foods seemed absolved of blame; the best explanation seems to be that nutritional disturbances promoted by heavy alcohol consumption make the otherwise resistant esophagus almost as vulnerable as the bronchi to tobacco smoke carcinogens.

Also dealing with tobacco, Cowdry and his associates report that radiation and cigarette tar have additive carcinogenic effects—what we gain with filters we probably lose to fall-out from atomic explosion testing.

A constructive use for radiation is suggested by Hoye and Smith: They found that in an experimental setting preoperative radiation reduced the viability of tumor cells so that the incidence of metastases secondary to later surgery was significantly lower than when operation had not been preceded by such treatment. [*This is a possible explanation of the efficacy of preoperative radiation in the combined treatment of human rectal cancer.*—J. W. B.] But radiotherapy can have many complications. Koss et al. report seven cases of cervical-vaginal in situ carcinoma following radiation control of cervix cancer.

In three articles, Moertel, Dockerty and Baggenstoss present the Mayo Clinic data on multiple primary cancers. The total incidence was 5.1%; when multiple cancers of the same tissue were excluded, it was 2.8%. If no strong general tendency to susceptibility and no polyoma viral effect is demonstrated, at least it is clear that, contrary to some reports, having one cancer is no protection against the coming of a second. Furthermore, since there was a 150% increase in cancers occurring before the age of 50 in the relatives of patients with multiple cancers, some genetic susceptibility is suggested.

Radical surgery, properly used in properly selected patients, is an effective method of palliation of unresectable ovarian cancer in Brunschwig's experience. The primary indication was intestinal obstruction due to tumor. Some palliation and increase in life was achieved in 40% of 65 patients operated on by this means. Sixteen lived more than a year, and five were five-year survivors!

Cliffton and Grossi report that dornase is a particularly effective treatment in the dread postoperative complication of tracheitis sicca as well as for the less deadly but more common lobar atelectasis.

Adrenal steroids not only may produce gastric ulceration but Hartman and Sherlock report that with their use there is a marked increase in metastases of breast cancer to the stomach. This was an important point since in several instances this metastatic site was the source of fatal hemorrhage.

at a glance . . .

abstracts of the current literature on cancer . . .

Lymphosarcoma: Effects of Therapy

Doctors Rosenberg, Diamond and Craver report on the effects of treatment and survival in 1269 cases of lymphosarcoma at Memorial Center for Cancer and Allied Diseases. All were diagnosed histologically and an attempt was made to eliminate all cases of leukemia either by peripheral blood smears or by sternal puncture, when indicated. Of these patients, 7.6 per cent developed lymphocytic leukemia and are included in the study. Leukemia may develop from all three types of lymphosarcoma. These types and the number in this study are: Giant follicular lymphosarcoma, 162; reticulum cell sarcoma, 554; lymphosarcoma, 553. Hodgkin's disease is not considered one of the variants. The disease occurs at any age, with the greatest number of cases occurring in the fifth decade with a male to female ratio of 1.7 to 1.0. Patients' response to therapy was evaluated over a one- to four-week period and it was found that, with radiation treatment, 75 per cent benefited immediately from the first and second course of therapy. Subsequently, resistance to radiation developed. Alkylating agents for example, nitrogen mustard, gave a 19 per cent improvement initially and 10 per cent with the second course of therapy. Antimetabolite drugs, such as folic acid and purine antagonists, produced some improvement in 29 per cent. Adrenal steroids and ACTH, in 8 per cent of patients, gave some improvement, lasting maximally for seven weeks. These drugs were helpful in treating hemolytic anemia and hemorrhages, when present. Systemic effects, i.e., reduction of pain, weight gain and a sense of well being, were noted. Radioactive phosphorus helped 14 per cent of patients and they were generally those who developed lymphocytic leukemia. Surgical treatment of localized disease has been helpful in some cases; however, because of the multicentric origin of this disease, its value is limited. At times a combination of therapy was indicated, for example, hemolytic anemia occurring in a patient with lymphosarcoma was treated by steroids plus radiation. In cases of pressure on vital organs, an

alkylating agent prior to radiation was used.

Those with giant follicular lymphosarcoma fare much better than those with reticulum cell sarcoma and lymphosarcoma. Of these latter two there is a slightly better prognosis in those with lymphosarcoma. It is believed that patients with an absolute lymphocytopenia have a poorer prognosis. The presence of this is probably related to widespread disease as well as previous radiation and/or chemotherapy. Children have a poorer prognosis than adults. The treatment of choice is still radiation and the overall survival rate for five years is 28.4 per cent.

Rosenberg, S. A.; Diamond, H. D., and Craver, L. F.: Lymphosarcoma; the effects of therapy and survival in 1,269 patients in a review of 30 years' experience. Ann. Int. Med. 53:877-897, Nov., 1960.

Circulating Tumor Cells

Circulating tumor cells were found in 18 per cent of 247 peripheral blood specimens obtained from 36 patients with nonresectable malignant melanoma.

Twenty-five of 36 patients (70 per cent) studied in this category demonstrated tumor cells in 1 or more peripheral specimens.

A direct relationship was found between the rate of growth or appearance of new metastatic nodules and the finding of peripheral circulating tumor cells.

A greater frequency of positive specimens and patients with positive specimens was found in the late months of life.

Results of circulating tumor cell studies in 6 surgical patients are presented.

—AUTHORS' SUMMARY

Rohmsdahl, M. M.; Potter, J. F.; Malmgren, R. A.; Chu, E. W.; Brindley, C. O., and Smith, R. R.: A clinical study of circulating tumor cells in malignant melanoma. Surg. Gynec. & Obst. 111:675-681, Dec., 1960; p. 681.

Scirrhous Carcinoma of the Colon and Rectum

Ninety-one cases of primary scirrhous adenocarcinoma of the colon and rectum have been studied clinicopathologically. Three pathologic prototypes were delineated: In 11 cases the lesions presented the rare "linitis-plastica" type of configuration; in 29 they were stenosing "napkin-ring" cancers, and in 51, ulcerative growths definable only on the basis of microscopic evidence of pronounced desmoplasia.

The scirrhous reaction appeared to be excited by the neoplastic cells themselves. It seemed to be a property possessed principally by certain anaplastic tumors, the involved lymph nodes and visceral metastatic lesions which maintained the scirrhous pattern. Other primary cancers in the same hosts were never desmoplastic.

The growths were unusually aggressive. Perineural and venous involvement was frequently observed, nodes were often invaded, and a high incidence of hepatic metastasis limited many resections to the palliative category. The average small size of the growths is paradoxic in this over-all picture.

A completely accurate prediction of results of treatment was not possible from this small series. The trend indicated, however, is disappointing.

—AUTHORS' SUMMARY

Fahl, J. C.; Dockerty, M. B., and Judd, E. S.: Scirrhous carcinoma of the colon and rectum. Surg. Gynec. & Obst. 111:759-766, Dec., 1960; pp. 765-766.

New Treatment of Carcinoma of the Adrenals

Initial observation of animals demonstrated that the insecticide DDD, or Rothane, caused a selective necrosis of the zona fasciculata and zona reticularis of the adrenal cortex which resulted in an associated adrenal insufficiency. The ortho, para prime isomer of

crude DDD was developed for clinical use. The authors have used this preparation in 18 patients with histologically proven adrenocortical cancer with metastases. The usual dose of 10 grams a day was administered from four to eight weeks. Toxic reactions were noted in the gastrointestinal tract, the skin, and in the central nervous system as depression and muscular tremors. All toxic reactions were reversible with either a lowering of the dosage of the drug or stopping it. No toxicity was noted in the liver, kidneys or bone marrow. In seven patients, objective decrease of evidence of metastatic lesions was obtained. Seven additional patients showed a significant steroid suppression while four showed no effect. The authors believe that the drug, with its specific effect, is unique. Although being quite similar to amphenone, the latter differed from it in that a reduction in steroid excretion was not associated with any effect on tumor growth. They also speculate that all patients with adrenocortical carcinoma who have been operated upon should be given o,p'DDD at the first sign of increased steroid excretion even if no actual metastases are demonstrable.

Bergenstal, D. M.; Hertz, R.; Lipsett, M. B., and Moy, R. H.: Chemotherapy of adrenocortical cancer with o,p'DDD. Ann. Int. Med. 53:672-682, Oct., 1960.

Splenectomy in the Treatment of Hypersplenism Due to Lymphoma and Leukemia

Thirty-six patients with lymphosarcoma, leukemia, Hodgkin's disease, and agnogenic myeloid metaplasia were splenectomized. Hypersplenism and, in two cases, symptomatic splenomegaly were the reasons for the procedure.

All patients were previously treated with alkylating agents, radiation, and steroids, alone or in combination.

There was an immediate 8% postoperative fatality and an additional 19% showed either a hemorrhagic or thrombotic phenomenon in the immediate postoperative period. Anticoagulation is indicated if a marked elevation of platelets occurs during the postoperative period.

Six of 33 patients showed no improvement with the treatment. The remaining ones showed the following responses: Significant improvement in one or more of the previously depressed blood elements; disappearance of symptoms related to the enlarged spleen; decrease in transfusion requirements; and ability to successfully reinstitute previously used methods of treatment.

Strawitz, J. G.; Sokal, J. E.; Grace, J. T., Jr.; Mukhtar, F., and Moore, G. E.: Surgical aspects of hypersplenism in lymphoma and leukemia. Surg. Gynec. & Obst. 112:89-95, Jan., 1961.

Acute Necrotizing Colitis

Thirteen cases of acute necrotizing colitis proximal to carcinomas of the colon producing partial obstruction of varying degrees are reported. The existence of this complication should be suspected if pain, tenderness, spasm, presence of a mass, tachycardia, or hyperpyrexia are present preoperatively.

The degree of inflammation varies from an edematous state to necrotic ulceration and perforation. The resected specimen should always be examined at the time of operation. If colitis is found, then a more extensive resection, exteriorization of the colonic limbs, or anastomosis with a proximal diverting colostomy should be performed. The procedure selected depends upon the extent of the disease and the condition of the patient.

—AUTHORS' SUMMARY

Hurwitz, A., and Khafif, R. A.: Acute necrotizing colitis proximal to obstructing neoplasms of the colon. Surg. Gynec. & Obst. 111:749-752, Dec., 1960; p. 752.

Adenocarcinoma of the Large Bowel

The prognosis in carcinoma of the large intestine is, in the opinion of the author, poorer than might be inferred from current medical literature. Emphasis on results of treating selected patients tends to obscure the fact that most patients will not achieve a five-year survival. More extensive excision might reduce the frequency of recurrences but tends to meet with opposition from both surgeons and patients; earlier treatment is endorsed by both cancer societies and physicians but depends on the alertness and cooperation of the patient. The signs and symptoms of intestinal cancer, although known to nearly every physician, often go unrecognized by the patient as long as six months before diagnosis is made. Intestinal cancer would probably be curable in the average case if patients could be taught the basic facts and conducted themselves accordingly.

—JOURNAL'S SUMMARY

—INTERLINGUA TRANSLATION—

Le prognosis in carcinoma del intestino grande es, in le opinion del autor, pejor que on infererea ab le literatura medical hodierne. Emphase super resultatos de tractar patientes seligite tende obscurar le facto que le major parte del patientes no seligite non supervivera cinque annos. Un excision plus extensive poterea reducer le frequentia de recurrentias ma tende incontrar opposition e del chirurgo e del patientes; tractamento plus prompte es indorsate per e societates de cancere e medicos ma depende del allertitate e cooperation del patiente. Le signos e symptomas de cancere intestinal, ben que cognoscite a quasi cata medico, frequentemente son incognite per le patiente usque sex menses ante que on face le diagnose. Cancere intestinal esserea probabilemente curabile in le caso medie si patientes poterea esser instruite e se conducerea ita.

Gilbertsen, V. A.: Adenocarcinoma of the large bowel; factors seemingly responsible for unrealistically optimistic appraisals of current curative achievements, and a suggestion for improvement of therapeutic results. J.A.M.A. 174:1789-1793, Dec. 3, 1960; p. 1789.

Lymphatic Studies in Carcinoma of the Rectum

Lymphatic pathways from the anus and rectum to the female genitalia were mapped out by means of vital dye studies in order to clarify the high incidence of residual carcinoma in the female genitalia after resection for carcinoma of the rectum and anus.

For carcinoma of the anal canal, the lymphatic map indicates that excision of the lower two thirds of the posterior vaginal wall should be added to abdominoperineal resection of the rectum.

For carcinoma of the lower part of the rectum, hysterectomy, oophorectomy, and excision of the broad ligaments and posterior vaginal wall should be added, in continuity, to abdominoperineal resection of the rectum.

For carcinoma of the midrectum, the same procedure is indicated, except that only the upper one third of the posterior part of the vaginal wall would need to be removed.

For carcinoma of the upper part of the rectum and rectosigmoid, the lymphatic map indicates that anterior resection is an adequate operation.

—AUTHORS' SUMMARY

Block, I. R., and Enquist, I. F.: Lymphatic studies pertaining to local spread of carcinoma of the rectum in the female. Surg. Gynec. & Obst.: 112:41-46, Jan., 1961; p. 46.

The Management of Pain Due to Malignant Disease

Pain due to malignant disease is usually not as severe as that due to benign conditions such as renal colic, tabetic crises and dermal burns. However, the duration of the pain is usually much longer.

Change in pain distribution in cases with malignant disease should make one suspicious of the extension of this process, even if it can not be demonstrated on physical examination, by X-ray study or by laboratory investigation.

In patients studied with symptomatic metastatic disease to bone, intervals of four weeks to 18 months may have to pass before roentgenologic evidence of the metastatic process may be obtained.

It is thus recommended that patients, especially over the age of 40 whose complaints suggest either the presence of an undiagnosed cancer or a metastatic process from a previously proven cancer, should be very carefully and thoroughly evaluated every six weeks. By 18 months the etiology of the complaint, if it is due to cancer, should be clarified. The distribution and quality of the pain will depend upon the involved organ as well as the adjacent structures.

The use of nonnarcotic analgesics such as aspirin, anacin, darvon, etc., alone or in combination with sedatives or tranquilizers, was found to be effective in most patients. In studying 971 patients, the author found it feasible to divide them into three groups. In those with a prognosis of less than three months, the goal of treatment was primarily one of comfort. No major surgical procedure or excess radiation was recommended. Occasional nerve blocks were used in this group. Another group consisted of those with a life-expectancy of three to 12 months, in whom pain was the chief factor interfering with their daily existence. Along with nonnarcotic analgesics, various neurosurgical procedures should be considered, e.g., spinothalmic tractotomies, stellate blocks, subarachnoid alcohol blocks and ganglionectomies. When the life-expectancy was over 12 months, various hormones, nonnarcotic analgesics, surgery, radiation, chemotherapy and other measures directed along curative lines were used.

In the use of narcotics, the authors found that there was very little significant difference among the commonly used drugs. They obtained the most satisfying results by using one narcotic drug for a period of three weeks, then stopping it, using a non-narcotic analgesic for one week and then reinstituting treatment with a different narcotic for another three week cycle. The obvious dangers of addicting a person who may have a long-term survival rate are mentioned.

Hypnosis and lobotomy have a questionable value in the management of patients with malignant disease. Supportive psychotherapy is obviously indicated.

Perese, D. M.: How to manage pain in malignant disease. J. A. M. A. 175:75-81, Jan. 14, 1961.

Squamous Carcinoma of the Lip

One hundred twenty-four consecutive cases of squamous carcinoma of the lip are analyzed.

Sixty-five cases with clinically uninvolved nodes had "prophylactic" bilateral suprahyoid neck dissections. Four of these had histologically proven metastases (6%).

The net and absolute five-year cures of this series were comparable to another series where "prophylactic" dissections were not done but careful follow up carried out.

If good follow up is possible routine "prophylactic" neck dissection is not recommended.

The bi-lobed flap of Zimany is useful in repairing many large defects of the lips.

—AUTHORS' SUMMARY

Lyall, D., and Grier, W. R. N.: Experiences with squamous carcinoma of the lip with special reference to the role of neck dissection. Ann. Surg. 152: 1067-1070, Dec., 1960; p. 1070.

Detection of Cancer

Results of 33,224 examinations of 9,123 patients were analyzed in a search for factors that might be especially helpful in the early diagnosis of

various forms of cancer. A total of 163 cases of cancer of the breast, stomach, large intestine, prostate, ovary, and uterus were thus studied. There was no significant difference in the symptoms, signs, or laboratory findings leading to the identification of malignancies in patients at their first examination as compared with later yearly reexaminations. A marked decrease in the incidence of cancer of the rectum was noted in patients seen at yearly intervals. In 15 of 21 cases of cancer of the breast the tumor nodule had not been noticed by the patient. These facts suggest that yearly examinations can bring about the earlier detection of cancer and lead to the more frequent removal of precancerous lesions.

—JOURNAL'S SUMMARY

—INTERLINGUA TRANSLATION—

Resultatos de 33,224 examines de 9,123 patientes esseva analysate in un recerca pro factores que pote esser specialmente servicial in le diagnose prompte de formas varie de cancere. Un total de 163 casos de cancere del mamma, gastro, intestino grande, prostata, ovario, e utero esseva studiate ita. Il non habeva differentia significative in le symptomas, signos, o trovatas laboratori menante al identification de malignitates in patientes al tempore de lor prime examine como comparate con re-examines annual plus tarde. Un diminution marcate in le incidentia de cancere del recto esseva notate in patientes vidite a intervallos annual. In 15 ex 21 casos de cancere del mamma le nodulo tumoral non habeva essite notate per le patiente. Iste factos suggere que examines annual pote effectuar le detection plus precoce de cancere e menar al extirpation plus frequente de lesiones precancerose.

Jenson, C. B.; Shahon, D. B., and Wangensteen, O. H.: Evaluation of annual examinations in the detection of cancer; special reference to cancer of the gastrointestinal tract, prostate, breast, and female generative tract. J.A.M.A. 174:1783-1788, Dec. 3, 1960; p. 1783.

Leukemia in Pregnancy

Doctors Frenkel and Meyers of the University of Michigan Medical Center report on eight pregnant patients who have leukemia, as well as reviewing additional adequately reported cases. They conclude that leukemia has no effect on pregnancy and pregnancy has no effect on leukemia. Routine obstetrical procedures should be followed and an attempt to interrupt the pregnancy because of an associated leukemic state is not indicated.

The treatment of the leukemia will vary as to the stage of the disease. Steroids are indicated when a bleeding tendency secondary to the leukemia develops. The use of antimetabolites, according to one group, is contraindicated while the authors believe they can be administered after the first trimester of pregnancy.

There have been no reports of any congenital abnormalities or bleeding dyscrasias in the children of those mothers who had received steroids and/or antimetabolites during their pregnancy. The immediate postpartum period has proved to be potentially dangerous to the mother and the use of antimetabolites and steroids may be lifesaving. The question of the newborn's need for steroids must be borne in mind, especially in those whose mothers have received steroid therapy during the pregnancy. If rapid deterioration of the child occurs, use of steroids is indicated.

Severe hypofibrinogenemia with hemorrhage may complicate the immediate postpartum period of the mother.

Frenkel, E. P., and Meyers, M. C.: Acute leukemia and pregnancy. Ann. Int. Med. 53:656-670, Oct., 1960.

not in sticks or stones

Recently, a distinguished physician who had been attending a number of cancer meetings, noticed that in all the discussions the patient was not mentioned or considered. It is somewhat of a paradox that the more that is done about the cancer problem and the closer it comes to being solved, the more remote the patient and his problems be come. The patient seems to be of less importance than his component parts. However, the cancer victim caught up in the terror and physical assault of the disease has only a slight concern for the composition of his chromosomes or the ratio of the DNA to RNA in his cells. Understandably, his main wish is to be surrounded and treated by the best and most skillful physicians available. Unfortunately, it appears that such services are likely to be less and less available to him. The trend seems to be in the other direction. Many of our best and most brilliant students are pursuing basic science studies which are far remote from the corporate *homo sapiens*, who is the real and central challenge of cancer.

Symptomatic of the patient's low priority in our schemes is the slight amount of professional interest manifested in genuine palliative therapy for incurable cancer patients. Similarly, the active interest in establishing criteria of inoperability, the fostering of inadequate operative procedures and the confusion engendered by jurisdictional therapeutic specialty vendettas, all indicate greater interest in methodology than in the patient. Other symptoms: Clinical cancer research involving patients has not thrived compared to other forms of cancer research; professional educational programs often carefully avoid being "burdened" by providing service to cancer patients.

The millions of dollars being raised and appropriated for cancer research are, of course, the greatest hope for the future, and the final solution can only come in this manner. Yet, what about the patient with cancer today?

Should more effort, funds, talent and imagination be directed toward him as a patient? Unfortunately, talent and funds for the effort against cancer are not an unlimited resource. Therefore, research and development programs for future gains against cancer must compete against needs for today's cancer victim. The problem is like that of the Joint Chiefs of Staff who are caught constantly between the demands for "pushbutton" weapons for the future, and men and guns for today's security. In fighting cancer, who are the Joint Chiefs of Staff? How shall it be decided what proportion of talent and funds the future or the present cancer victims shall have? While our hearts may be with the present, our minds know that today's successful treatment method was yesterday's dream, made a reality only by research.

Donated and appropriated funds reflect the public's wishes, and opinion surveys show that the higher a person is on the educational and economic scale, the more willingly he supports cancer *research* in preference to *service* for the cancer patient. Contrarily, those with low incomes and less education prefer to give their money and energy for care of the cancer patient. However, rich or poor, schooled or unschooled, all of us must remember that

the cancer patient is the cause of our concern.

If cancer existed only in sticks or stones, the great scientific race to control cancer in basic science laboratories and the great gifts and appropriations would be virtually nonexistent. This generosity, this overwhelming interest arises primarily because someone dearly beloved was, or is, a cancer victim. Thus, the hearts and the treasures of the people have been opened to those with cancer. These victims have provided, and continue to provide, both the inspiration and the perspective so necessary in fighting cancer. At this very moment, there are 785,000 Americans among us who know the terror of cancer as only victims can, and they need no convincing that the patient is both the cause and the goal of all our cancer control efforts.

Roald M. Israel

Exfoliative Cytology Booklet

The American Cancer Society announces the publication of a booklet on exfoliative cytology in the detection of cancer in various sites of the body. The booklet consists of reprints of papers, including color plates, which first appeared as a series in the 1960 issues of *CA*.

Copies will be available from the Divisions of the American Cancer Society.

COMING MEDICAL MEETINGS

Date 1961	Meeting	City
Apr. 13-14	James Ewing Society Dr. Theodore Miller 444 E. 68th St. New York 21, N. Y.	New York City
Apr. 16-20	American Society of Maxillofacial Surgeons Dr. Edward C. Hinds P. O. Box 20068 Houston 25, Texas	New York City
Apr. 30	American Federation for Clincal Research James E. Bryan 250 West 57th St. New York, New York	Atlantic City
May 2-3	Association of American Physicians Dr. Paul B. Beeson Yale University School of Medicine New Haven 11, Conn.	Atlantic City
May 2-3	American Pediatric Society Conrad M. Riley Denver General Hospital Denver 4, Colo.	Atlantic City
May 3-6	American Goiter Association, Inc. Dr. John C. McClintock 702 Madison Avenue Albany 8, N. Y.	Philadelphia
May 5-6	Society of Neurological Surgeons Dr. Guy L. Odum Duke University Medical Center Durham, N. C.	Boston
May 5-7	American Society of Internal Medicine Mr. G. Tod Bates 350 Post Street San Francisco 8, California	Miami Beach
May 8-12	American College of Physicians Dr. Edward C. Rosenow, Jr. 4200 Pine Street Philadelphia 4, Pa.	Miami Beach
May 11-13	American Radium Society Dr. Charles G. Stetson Englewood, N. J.	Colorado Springs
June 25-30	American Medical Association Dr. F. J. L. Blasingame 535 N. Dearborn St. Chicago 10, Ill.	New York City

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THE AMERICAN CANCER SOCIETY

is dedicated to saving lives from cancer and spearheads the fight against cancer quackery. Its Committee on New or Unproved Methods of Treatment of Cancer has a membership of physicians, lawyers, educators, and public relations specialists. This committee has been a prime mover in developing constructive action

against cancer quackery

Inspired by model legislation formulated by this committee with the active cooperation of the California Medical Association, California, Kentucky and Nevada recently passed bills providing the first effective means of fighting cancer quackery at its base of operations—in the local community.

To keep both the public and the medical profession informed, the Society has established, in its national office, a central repository of material on new or unproved methods of cancer diagnosis, treatment and cure—a principal source of such information in this country.

The American Cancer Society, in this as in all its efforts, serves both the private citizen and the practicing physician—and is, in turn, served by both.

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